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(56), (58) continued overleaf

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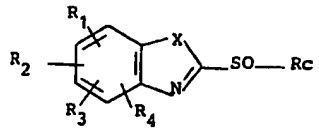
(54) Heterocyclic sulphinyl compounds

(57) Mainly novel compounds of formula I,



I

in which Rc is a nucleophilic nitrogen, oxygen or sulphur separated from the SO group by 1, 2, 3, 4 or 5 other atoms,

R_1, R_2, R_3 and R_4, which may be the same or different, are each hydrogen, halogen, alkoxy, alkyl, fluoroalkyl, acyl, $RS(O)_n-$, $-NO_2$, $-N(R)_2$, -NHCOR, or -COOH or an ester or amide thereof,

or an adjacent pair of R_1, R_2, R_3 and R_4 may in addition to the values given above, together form a chain $-(CH_2)_x-$ or, together with the carbon atoms to which they are attached, form a 6 membered unsaturated carbocylic or nitrogen heterocyclic ring,

x is 3, 4 or 5,

n is 0, 1 or 2,

X is O, S or NR_{15},

R_{15} is hydrogen, -COR, -COOR or alkyl which latter is optionally substituted by -OCOR,

R is phenyl, or alkyl optionally substituted by phenyl, the phenyl groups in turn optionally being substituted by alkyl,

and pharmaceutically acceptable salts thereof are used as pharmaceuticals, e.g. to treat gastric acid secretion. The corresponding thioethers are also claimed.

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Formulae in the printed specification were reproduced from drawings submitted after the date of filing, in accordance with Rule 20(14) of the Patents Rules 1982.

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(58) Field of search
C2C

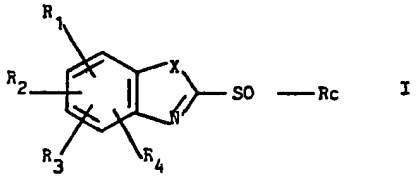
SPECIFICATION

Het r cyclic c mpounds

This invention relates to new compounds, methods for their preparation and pharmaceutical formulations containing them.

A variety of benzothiazole-2-sulphinamides are known for use as vulcanisation accelerators, e.g. from US Patents Nos 2,585,155 and 3,541,060, from French Patents Nos 1,003,821 and 2,037,001, and from German OLS 1,949,615. A number of 2-(pyridylmethylsulphinyl) benzimidazoles are known for use as pharmaceuticals from European Patent Applications Nos 5129 and 80602 and from British Patent Application No 2,134,523 and a number of 2-(heterocyclicmethylsulphinyl)benzimidazoles are known from Swiss Patent 623,582, West German OLS 2,548,340 and French Patent 2,392,021.

According to the invention we provide compounds of formula I,



I

in which Rc is a nucleophilic nitrogen, oxygen or sulphur separated from the SO group by 1, 2, 3, 4 or 5 other atoms,

R_1, R_2, R_3 and R_4, which may be the same or different, are each hydrogen, halogen, alkoxy, alkyl, fluoroalkyl, alkanoyl, $RS(O)_n-$, $-NO_2$, $-N(R)_2$, -NHCOR, or -COOH or an ester or amide thereof,

or an adjacent pair of R_1, R_2, R_3 and R_4 may in addition to the values given above, together form a chain $-(CH_2)_x-$ or, together with the carbon atoms to which they are attached, form a 6 membered unsaturated carbocylic or nitrogen heterocyclic ring,

x is 3, 4 or 5,

n is 0, 1 or 2,

X is O, S or NR_{15},

R_{15} is hydrogen, -COR, -COOR or alkyl which latter is optionally substituted by -OCOR,

R is hydrogen, phenyl, or alkyl optionally substituted by phenyl, the phenyl groups in turn optionally being substituted by alkyl,

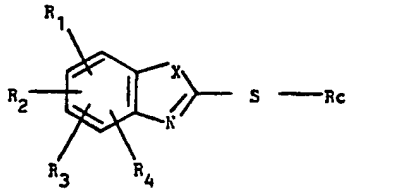
provided that i) Rc is not $-CH_2CH_2$-morpholino, ii) that when Rc is a nitrogen nucleophile carried on an aryl or heteroaryl group R_{15} is not a group -COR in which R is unsubstituted alkyl, iii) when X is NR_{15} Rc does not comprise an unsaturated nitrogen heterocyclic ring other than such a ring substituted by either a) a substituted or unsubstituted amino group, or b) an N-oxido group, and iv) when X is NR_{15} Rc does not comprise an alkyl group substituted by an optionally alkyl or halo substituted piperidino group,

and pharmaceutically acceptable salts thereof.

We also provide the compounds of formula I without proviso ii) and pharmaceutically acceptable salts thereof, for use as pharmaceuticals, and without provisos i) and ii) for use in the prevention or inhibition of gastric acid secretion.

According to the invention we also provide a process for the production of a compound of formula I, or a pharmaceutically acceptable salt thereof, which comprises

a) selective oxidation of a corresponding compound of formula VI,



VI

in which R_1, R_2, R_3, R_4, X and Rc are as defined above,

b) production of a compound of formula I in which X is NR_{15} and R_{15} is as defined above save that it cannot be hydrogen, by reaction of a corresponding compound of formula I in which R_{15} is hydrogen with a compound $R_{15}Z$ in which R_{15} is as defined above save that it cannot be hydrogen, and Z is a good leaving group, or

c) production of a compound of formula I carrying an $-NH_2$ group by selective reduction of a corresponding compound of formula I carrying an $-NO_2$ group,

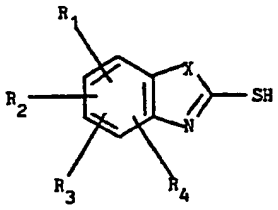
and where desired or necessary converting the resulting compound of formula I to a pharmaceutically acceptable salt thereof, or vice versa.

The oxidation of process a) may be carried out in a solvent which is inert under the reaction conditions, e.g. ethyl acetate, dichloromethane, chloroform or a mixture thereof. The reaction is preferably carried out at less than room temperature, e.g. −20° to +10°C. Suitable oxidising agents for use in the reaction are peracids, e.g. *m*-chloroperbenzoic acid or t-butylhydroperoxide in the presence of a suitable catalyst, e.g. vanadyl acetyl acetonate.

In process b) the good leaving group may be, for example, halogen and the reaction may be carried out in a solvent which is inert under the reaction conditions, e.g. dimethylformamide, in the presence of a base and at a temperature of from about 15° to 30°C.

In process c) the selective reduction may, for example, be carried out chemically under basic conditions, e.g. using hydrazine and Raney nickel, but is preferably carried out catalytically, e.g. using a PtO_2 catalyst and ethanol as the reaction medium.

The compounds of formula VI may be made by conventional processes known *per se*, e.g. by reaction of a compound of formula VII,



VII

in which R_1, R_2, R_3, R_4 and X are as defined above, with a compound of formula VIII,

Z–Rc VIII

in which Rc is as defined above, and

Z is a good leaving group, e.g. halogen (chlorine).

The reaction may be carried out in a suitable solvent, e.g. N,N-dimethylformamide, and in the presence of an acid acceptor, e.g. potassium carbonate.

The compounds of formulae VII and VIII are either known or may be made from known compounds using conventional techniques known *per se*. The production of the starting materials for the above reactions is more fully described in British Patent Application No 85/09406 from which the present case draws priority.

The compounds of formula I, and the intermediates therefor, may be isolated from their reaction mixtures using conventional techniques.

Pharmaceutically acceptable salts of the compounds of formula I include salts with suitable organic or inorganic acids, e.g. with a hydrohalic, sulphuric, alkanesulphonic, tartaric or citric acid. We also provide, when the compound of formula I carries a –COOH, or other acidic, group, salts with suitable organic or inorganic bases, e.g. ammonium, alkali metal, alkaline earth metal, alkylamino, etc. salts. The benzimidazole nucleus itself is acidic and can form salts with appropriate bases as above.

The compounds of formula I, and pharmaceutically acceptable salts thereof, are useful because they possess pharmacological activity in animals; in particular they are useful because they prevent or inhibit gastric acid secretion, e.g. in the test set out in Am.J.Physiol., 1982, *243*(6), G505–510. The compounds of formula I are also useful as intermediates in the synthesis of other chemicals.

The new compounds are thus indicated for use in the prevention or inhibition of gastric acid secretion, and/or the treatment of conditions normally involving excess gastric acid secretion, e.g. peptic, duodenal, gastric, recurrent or stormal ulceration, dyspepsia, duodenitis, Zollinger-Ellison syndrome, reflux oesophagitis and the management of haemorrhage, e.g. from erosion of ulcers in the upper gastrointestinal tract, especially when a major blood vessel is not involved. The compounds may also be used to treat gastritis or dyspepsia associated with administration of non-steroidal anti-inflammatory drugs, in the prophylaxis of gastrointestinal haemorrhage from stress ulceration in seriously ill or burned patients, in the prophylaxis of recurrent haemorrhage in patients with bleeding peptic ulcers, before general anaesthesia in patients at risk of acid aspiration syndrome (Mendelson's syndrom) and to reduce the chance of haemorrhage in patients with leukaemia, graft versus host disease or with severe hepatic failure. The above conditions may be treated whether or not they are associated with excess gastric acid secretion.

Patterns of therapeutic use which may be mentioned are :–

a) a high dose initially, for say 2–4 weeks, followed by low-dose maintenance therapy after the condition has improved, e.g. the ulcer has healed,

b) as in a) above, but the maintenance therapy including a cytoprotective agent, e.g. a PGE_2 derivative,

c) combination therapy, using a low dose of the compound of the inv ntion in associati n with a low, well-tolerated dose of a cytoprotectant and/or antacid,

d) intermittent dosing, e.g. every second day, may be appropriate as maintenance therapy.

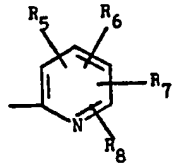
For the above mentioned uses the dosage administered will, of course, vary with the compound employed, the mode of administration and the treatment desired. However, in general, satisfactory results are obtained when the compounds are administered at a dosage of from 10^{-6}M to 10^{-4}M in the test set out in Am.J.Physiol, 1982, *243* (6), G505–G510. For man the indicated total daily dosage is in the range of from about 1mg to 3,000mg, preferably 5 to 500mg, and more preferably from about 10mg to 200mg, which may be administered in divided doses from 1 to 6 times a day or in sustained release form. Thus unit dosage forms suitable for administration comprise from about 1.0mg to 600mg of the compound admixed with a solid or liquid pharmaceutically acceptable diluent, carrier or adjuvant.

The compounds of formula I, and pharmaceutically acceptable salts thereof, have the advantage that they are more readily absorbed, or are less irritant to the GI tract, or have less toxic side effects, or are more active, or are more stable to gastric acid when administered by ingestion than compounds of similar structure.

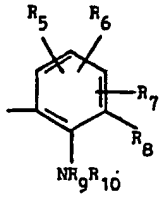
The nucleophile which is part of the group Rc is preferably separated from the SO group by 4, or more preferably 3 or 2 atoms and those atoms are preferably carbon atoms. The nucleophile which is part of the group Rc is such as to be be able to express its nucleophilicity under normal physiological conditions, e.g. at a pH of from about 7.4 to 1, and which in those conditions is more nucleophilic than water. The nucleophile is also preferably basic and the degree of protonation of the nucleophile will be related to the pH. However, there will always be a significant population of unprotonated nucleophile even at a low pH.

Particular nucleophiles which may be mentioned include the oxygen of pyridine oxide or phenolic OH, the sulphur of a thioether or of a thiophenol or a precursor therefor, e.g. a thioester. However we prefer the nucleophile to be a nitrogen nucleophile (in which the nitrogen atom carries no charge). We particularly prefer the nitrogen nucleophile to be in the form of an oxime, hydrazine, pyridine or most preferably amine group. The amine group may optionally be substituted, e.g. by groups R_9 and R_{10} as defined below, and is preferably carried on an aromatic ring system, e.g. on a benzene ring.

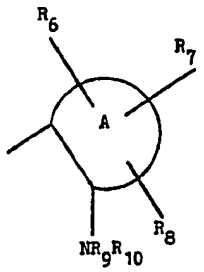
Groups Rc which may be mentioned include those of formula $-C(R_{16}R_{17})_y-(CR_{18}R_{19})_z-Rx$ in which y and z, which may be the same or different, are each 0, 1 or 2; R_{16}, R_{17}, R_{18} and R_{19}, which may be the same or different, are each hydrogen or alkyl, and Rx is a ring of formula II, III, IV or V,



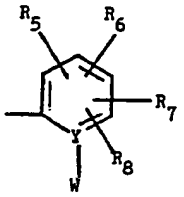
II



III



IV



V

and, when y + z is not 0, Rx may be $-NR_9R_{10}$,

R_5, R_6, R_7 and R_8 are selected from the significances defined above for R_1, R_2, R_3 and R_4,

R_9 and R_{10}, which may be the same or different, are each hydrogen, alkyl, phenyl or cycloalkyl each of which may optionally be substituted by phenyl, the phenyl groups in turn optionally being substituted by alkyl,

or one of R_9 and R_{10} may be as defined above and the other may be $-OR_{11}$ or $-NR_{12}R_{13}$, or

R_9 and R_{10}, together with the nitrogen atom to which they are attached may form a saturated or unsaturated 4 to 8 inclusive membered ring which may contain 0, 1 or 2 further hetero atoms, which ring may carry one or more substituents R_1, and

R_{11}, R_{12} and R_{13}, which may be the same or different, each represent hydrogen, alkyl optionally substituted by halogen or by $=O$, cycloalkyl, alkanoyl, phenyl or pyridyl,

or R_9 is as defined above save that it cannot form a ring with R_{10}, and R_8 and R_{10}, together with the nitrogen atom and the carbon atoms of the ring to which the nitrogen atom and R_8 are attached, form a saturated 4 to 8 inclusive membered ring which may contain 0, 1, or 2 further hetero atoms, which ring may carry one or more substituents R_1,

A represents a 5 or 6 membered nitrogen or sulphur containing heterocyclic ring which is connected to the rest of the molecule through a ring carbon atom,

Y is N or C,

when Y is N, W is O^- and when Y is C then W is $-OH$ or $-SR_{14}$, and

R_{14} is hydrogen, phenyl, cycloalkyl, alkanoyl or alkyl optionally substituted by phenyl.

We prefer at least one of R_1, R_2, R_3 and R_4, and at least one of R_5, R_6, R_7 and R_8 to be other than hydrogen. When R_1, R_2, R_3, R_4, R_5, R_6, R_7 or R_8 is halogen it may be chlorine or fluorine.

When any of R_1 to R_8, R, X, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18} or R_{19} represent or contain a carbon containing group we prefer that group to contain up to and including 10 and preferably up to and including 6, carbon atoms.

We particularly prefer each of R_9 and R_{10} to contain 1 or 2 carbon atoms.

When R_9 and R_{10} together with the nitrogen atom to which they are attached form a ring, the ring may contain a further nitrogen, oxygen and/or sulphur atom. We prefer that ring to be a piperidino or morpholino ring.

We prefer ring A to be aromatic. Examples of ring A which may be mentioned are thiophene, pyrazole and preferably pyrimidine or pyridine.

The number of substituents R_5 to R_7 clearly cannot be more than the number of positions available for substitution on ring A.

When any of R_1 to R_8 represent an ester we prefer it to be with a C1 to 6 alcohol, e.g. with an alkanol. When any of R_1 to R_8 represent an amide they may be, for example, an unsubstituted or a mono- or di-alkyl substituted amide.

When an adjacent pair of R_1 to R_4 r R_5 to R_8 together form a chain we prefer that chain to b $-CH=CH-CH=CH-$ r $-(CH_2)_4-$.

Specific groups R_1 to R_4 include hydr gen, methoxycarb nyl, phenylcarbonyl, methyl, chloro, methoxy, CF_3, NO_2, *p*-toluenesulphonyl and $-NH_2$ or an adjacent pair of R_1 to R_4 may together form a $-CH=CH-CH=CH-$ chain.

We prefer y to be 0 and z to be 0 or 1. We also prefer R_{16}, R_{17}, R_{18} and R_{19} to be selected

from H and methyl, and more preferably for all t be H.

Specific non-cyclic groups Rc which may be mentioned ar $-CH_2CH_2N(CH_3)_2$ and $-CH_2CH_2N(CH_3)C_6H_5$.

Specific gr ups R_5 to R_8 include hydrogen, methyl, chloro, propyl, methoxyl and butyl.

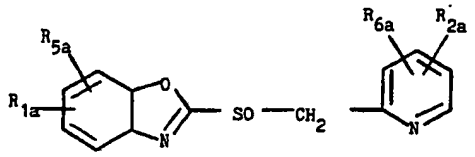
When R_8 and R_{10}, together with the nitrogen atom and the carbon atoms of the ring to which they are attached, form a ring, we prefer that ring to be a piperidino ring, e.g. an N-methyl piperidino ring.

Specific groups X are NH, O, S, Nacetyl, NCH_2OCOt-butyl, NCOOethyl and Nmethyl.

A specific group R_{14} is acetyl.

According to the invention we provide the following specific groups of compounds of formula I,

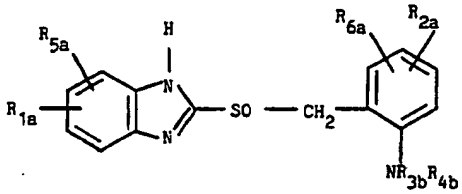
a)



Ia

in which R_{1a}, R_{2a}, R_{5a} and R_{6a}, which may be the same or different, are each hydrogen, halogen, alkoxy, alkyl, or –COOH or an ester thereof,

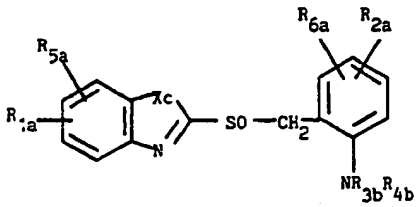
b)



Ib

in which R_{1a}, R_{2a}, R_{5a} and R_{6a}, are as defined above, and
R_{3b} and R_{4b}, which may be the same or different, are each hydrogen or alkyl,

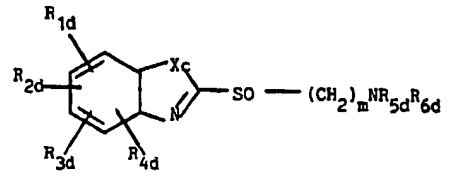
c)



Ic

in which R_{1a}, R_{2a}, R_{5a}, R_{6a}, R_{3b} and R_{4b}, are as defined above, and
Xc is NH, Nalkyl C1 to 6 O or S,

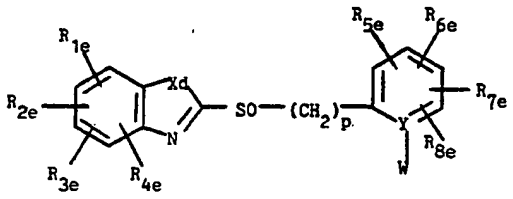
d)



Id

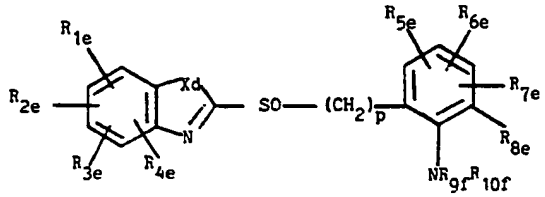
in which R_{1d}, R_{2d}, R_{3d} and R_{4d}, which may be the same or different, are each hydrogen, halogen, alkoxy, alkyl, fluoroalkyl, alkanoyl, $RdS(O)_n-$, or –COOH or an ester thereof,
or an adjacent pair of R_{1d}, R_{2d}, R_{3d} and R_{4d} may in addition to the values given above, together form a chain $-(CH_2)_x-$, $-CH=CH-CH=CH-$ or $-N=CH-CH=CH-$,
x, n and Xd are as defin d ab ve,
m is 1 or 2,
Rd is alkyl optionally substitut d by phenyl which in turn is optionally substituted by alkyl,
R_{5d} and R_{6d}, which may be the same or different, are each hydrogen or alkyl,
or one of R_{5d} and R_{6d} may be as defined above and the other may be $-OR_{11d}$ or $-NR_{12d}R_{13d}$, or R_{5d} and R_{6d}, t geth r with the nitrogen atom to which th y ar attach d, may form a saturated or unsaturated 4 to 8 inclusive membered ring which may contain 0, 1 or 2 further hetero

atoms, which ring may carry on or more substituents R_{1d}, and
R_{11d}, R_{12d} and R_{13d}, which may be th same or differ nt, each represent hydrogen, alkyl optionally substituted by halogen or = O, cycloalkyl, alkanoyl, phenyl or pyridyl,
e)



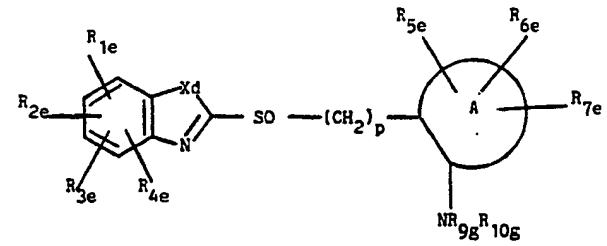
Ie

in which R_{1e}, R_{2e}, R_{3e}, R_{4e}, R_{5e}, R_{6e}, R_{7e} and R_{8e}, which may be the same or different, are each hydrogen, halogen, alkoxy, alkyl, fluoroalkyl, alkanoyl, $RdS(O)_n-$, or –COOH or an ester thereof, or an adjacent pair of R_{1e}, R_{2e}, R_{3e} and R_{4e} and/or an adjacent pair of R_{5e}, R_{6e}, R_{7e} and R_{8e} may in addition to the values given above, together form a chain $-(CH_2)_x-$, –CH = CH–CH = CH– or –N = CH–CH = CH–,
x, n, Xd and Rd are as defined above,
p is 0, 1 or 2,
Y is N or C,
when Y is N, W is O^- or $-NH^+$, and when Y is C then W is –OH or $-SR_{9e}$, and
R_{9e} is hydrogen, alkyl optionally substituted by phenyl, phenyl or cycloalkyl,
f)



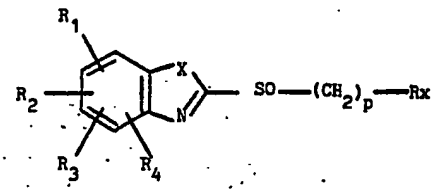
If

in which R_{1e}, R_{2e}, R_{3e}, R_{4e}, R_{5e}, R_{6e}, R_{7e}, R_{8e}, n, p and Xd are as defined above,
R_{9f} is hydrogen, alkyl or cycloalkyl each of which may optionally be substituted by phenyl, the phenyl in turn optionally being substituted by alkyl,
or R_{9f} may be $-OR_{11}$ or $-NR_{12}R_{13}$,
R_{11}, R_{12} and R_{13} are as defined above, and
R_{8f} and R_{10f}, together with the nitrogen atom and the carbon atoms of the benzene ring to which the nitrogen atom and R_{8f} are attached, form a saturated 4 to 8 inclusive membered ring which may contain 0, 1 or 2 further hereto atoms,
g)



Ig

in which A represents a 5 or 6 membered nitrogen or sulphur containing heterocyclic ring,
R_{1e}, R_{2e}, R_{3e}, R_{4e}, R_{5e}, R_{6e}, R_{7e}, Xd and p are as defined above,
R_{9g} and R_{10g}, which may be the same or different, are each hydrogen, alkyl or cycloalkyl each of which may optionally be substituted by phenyl, the phenyl in turn optionally being substituted by alkyl,
or one of R_{9g} and R_{10g} may b as defined above and the other may be $-OR_{11}$ or $-NR_{12}R_{13}$, or R_{9g} and R_{10g}, t g th r with th nitrogen at m to which th y are attach d, may form a saturated 4 to 8 inclusive m mb red ring which may contain 0, 1 or 2 further hetero at ms, which ring may carry one or more substituents R_{1e}, and
R_{11}, R_{12} and R_{13} are as defined above,
h)



Ih

in which R_1, R_2, R_3, R_4, X, p and Rx are as defined above save that when an adjacent pair of R_1, R_2, R_3 and R_4 and/or an adjacent pair of R_5, R_6, R_7 and R_8 together form a chain that chain is $-(CH_2)_x-$, $-CH=CH-CH=CH-$ or $-N=CH-CH=CH-$.

Certain of the compounds of formula VI are novel and the invention also provides these novel compounds. Of particular interest are compounds of formula VI in which y + z is more than 0 and in particular such compounds in which Rx is a ring of formula III.

According to our invention we also provide a pharmaceutical composition comprising (preferably a minor proportion of) a compound of formula I, or a pharmaceutically acceptable salt thereof, as active ingredient, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier. Examples of suitable adjuvants, diluents or carriers are:– for tablets and dragees; lactose, starch, talc or stearic acid; for capsules, tartaric acid or lactose; for suppositories, natural or hardened oils or wax; and for injections (i.m. or i.v.) or enemas water, surfactants and preservatives. The compounds may also be administered transdermally, e.g. in an ointment base. The compound of formula I, or the pharmaceutically acceptable salt thereof, preferably has a mass median diameter of from 0.01 to 10 microns. The compound of such particle size may be made by grinding or milling followed if necessary by particle size classification using, for example, a sieve. The compositions may also contain suitable preserving, stabilising, and wetting agents, solubilizers, sweetening and colouring agents and flavourings. The compositions may, if desired, be formulated in sustained release form.

The compounds may, if desired, be co-administered, with (e.g. as a mixture with) an antacid buffer.

We prefer compositions which are designed to be taken by ingestion or rectally and to release their contents in the intestine. We particularly prefer compositions which will pass through the acidic parts of the gastrointestinal tract unaffected, e.g. enteric coated formulations.

The compounds of formula I are optically active and may be resolved into their optical isomers using conventional techniques known *per se*. The invention therefore provides the compounds as their optical isomers, or as mixtures, e.g. racemic mixtures, thereof.

The invention is illustrated, but in no way limited by the following Examples in which temperatures are in degrees centigrade.

Example 1

N,N-Dimethyl 2-(1H-benzimidazol-2-ylsulphinylmethyl)benzenamine

a) *N,N-Dimethyl 2-(1H-benzimidazol-2ylthiomethyl)benzenamine*

2-Dimethylaminobenzyl chloride hydrochloride (8.18g) was dissolved in dry dimethylformamide (100ml), treated with 2-mercaptobenzimidazole (5.4g) and anhydrous potassium carbonate (11.0g) and the resulting mixture stirred at room temperature overnight. The reaction mixture was poured into water and extracted with ethyl acetate which was washed with water and dried over magnesium sulphate. The solvent was evaporated and the residue recrystallised from toluene to give 5.68g of a cream coloured solid. The product was eluted down a flash chromatography column with dichloromethane/ethyl acetate (9:1) as eluant to give a colourless solid mp 158–160°.

Elemental Analysis:
Found: C, 68.05, H, 6.09, N, 15.1, S, 11.34.
$C_{16}H_{17}N_3S$
Required: C, 67.8, H, 6.01, N, 14.85, S, 11.31%

b) *N,N-Dimethyl 2-(1H-benzimidazol-2ylsulphinylmethyl)benzenamine*

98% m-Chloroperbenzoic acid (0.67g) was added portionwise over a few minutes to a stirred solution of the product of step a) (1.0g) in dichloromethane (30ml) at 0°. The reaction mixture was stirred for 0.5h, washed with aqueous saturated sodium bicarbonate solution then brin and dried. The solvent was evaporated and the residue eluted down a flash chromat graphy column using dichl romethane/ thyl acetat (7:3) as eluant to give 0.6g of colourless s lid mp 120–121°.

Example 2

By the method described in Exampl 1, and using the appropriate starting materials, may be prepared the following compounds:

a) i) 2-(2-Pyridinylmethylthio)benzoxazol mp 46–47°.
ii) 2-(2-Pyridinylmethylsulphinyl)benzoxazole
Found: C60.31% H4.02% N10.91% S12.36%
$C_{13}H_{10}N_2O_2S$ requires C60.5% H3.88% N10.9% S12.4%
b) i) 2-(4-Methoxy-3,5-dimethyl-2-pyridinylmethylthio)benzoxazole. mp 127–8°.
ii) 2-(4-Methoxy-3,5-dimethyl-2-pyridinylmethyl sulphinyl)benzoxazole. mp 103–5°.
c) i) 2-(4-Methoxy-3,5-dimethyl-2-pyridinylmethylthio)benzoxazole. mp 124–5°.
ii) 2-(4-Methoxy-3,5-dimethyl-2-pyridinylmethyl sulphinyl)benzothiazole. mp 142–142.5°.
d) i) 5-Chloro-2-(2-pyridinylmethylthio)benzoxazole. mp 84–5°.
ii) 5-Chloro-2-(2-pyridinylmethylsulphinyl)benzoxazole. mp 91–3°.
e) i) Methyl 2-(2-pyridinylmethylthio)benzoxazole-5-carboxylate mp 85–7°.
ii) Methyl 2-(2-pyridinylmethylsulphinyl)benzoxazole-5-carboxylate. mp 87–90°.
f) i) 2-(2-Pyridinylmethylthio)benzothiazole. mp 52–3°.
ii) 2-(2-Pyridinylmethylsulphinyl)benzothiazole. mp 106–8°.
g) i) N,N-Dimethyl-2-(5,6-dimethyl-1H-2-benzimidazolylthiomethyl)benzenamine. mp 144–6°.
ii) N,N-Dimethyl-2-(5,6-dimethyl-1H-2-benzimidazolylsulphinylmethyl)benzenamine. mp 141–2°. mp 206–7°.
h) i) 2-(1H-2-Benzimidazolylthiomethyl)-N,N,4-trimethyl-benzenamine. mp 159–161°.
ii) 2-(1H-2-Benzimidazolylsulphinylmethyl)-N,N,4-trimethyl-benzenamine. mp 133–4°.
i) i) 2-(1H-2-Benzimidazolylthiomethyl)-4-chloro-N,N-dimethyl-benzenamine. mp 148–151°.
ii) 2-(1H-2-Benzimidazolylsulphinylmethyl)-4-chloro-N,N-dimethyl-benzenamine. mp 148–151°.
j) i) 2-(5-Chloro-1H-2-benzimidazolylthiomethyl),-N,N-dimethyl-benzenamine. mp 49–52°.
ii) 2-(5-Chloro-1H-2-benzimidazolylsulphinylmethyl)-N,N-dimethyl-benzenamine. mp 121–123°.
k) i) 2-(5,6-Dichloro-1H-2-benzimidazolylthiomethyl)-N,N-dimethylbenzenamine. mp. 128–130°.
ii) 2-(5,6-Dichloro-1H-2-benzimidazolylsulphinylmethyl)-N,N-dimethyl-benzenamine. mp. 147–9°.
l) i) Methyl 2-(2-dimethylaminophenylmethylthio)-1H-benzimidazole-5-carboxylate. mp 127–9°.
ii) Methyl 2-(2-dimethylaminophenylmethylsulphinyl)-1H-benzimidazole-5-carboxylate. mp 130° (decomp).
m) i) N,N-Dimethyl-2-(5-methyl-1H-2-benzimidazolylthiomethyl)benzenamine. mp 141–3°.
ii) N,N-Dimethyl-2-(5-methyl-1H-2-benzimidazolylsulphinylmethyl)benzenamine. mp 50–2°.
n) i) 2-[2-(1-Piperidyl)-phenylmethylthio]-1H-benzimidazole. mp 171–2°.
ii) 2-[2-(1-Piperidyl)-phenylmethylsulphinyl]-1H-benzimidazole. mp 160–1°.
o) i) 2-(1H-2-Benzimidazolylthiomethyl)-N,N-diethyl-benzenamine. mp 127–8°.
ii) 2-(1H-2-Benzimidazolylsulphinylmethyl)-N,N-diethyl-benzenamine. mp 109°.
p) i) 2-[2-(5-Methoxy-1H-benzimidazolyl)thiomethyl]-N,N-dimethyl-benzenamine. MS: M^+329.
ii) 2-[2-(5-Methoxy-1H-benzimidazolyl)sulphinylmethyl]-N,N-dimethyl-benzenamine.
Found: C60.36% H5.81% N11.89% S9.69%
$C_{17}H_{19}N_3O_2S \cdot {}^1/_7\, CH_2Cl_2$
reqs: C60.30% H5.65% N12.30% S9.38%
q) i) 2-(2-Benzothiazolylthiomethyl)-N,N-dimethylbenzenamine. mp 47–8°.
ii) 2-(2-Benzothiazolylsulphinylmethyl)-N,N-dimethyl-benzenamine. mp 72–3°.
r) i) 2-(5-Trifluoromethyl-1H-2-benzimidazolylthiomethyl)-N,N-dimethyl-benzenamine. mp 50–51°.
ii) 2-(5-Trifluoromethyl-1H-2-benzimidazolylsulphinylmethyl)-N,N-dimethyl-benzenamine. mp 50–51°.
s) i) N,N-Dimethyl-2-(5-nitro-1H-2-benzimidazolylthiomethyl)-benzenamine. mp 146–8°.
ii) N,N-Dimethyl-2-(5-nitro-1H-2-benzimidazolylsulphinylmethyl)-benzenamine. mp 105–6° (d).
t) i) [2-(2-N,N-Dimethylaminophenylmethylthio)-1H-5-benzimidazolyl]phenyl methanone. mp 62°.
ii) [2-(2-N,N-Dimethylaminophenylmethylsulphinyl)-1H-5-benzimidazolyl]phenyl methanone. mp 74°.
u) i) 2-(5,6-Dimethoxy-1H-2-benzimidazolylthiomethyl)-N,N-dimethyl-benzenamine. mp 93–5°.
ii) 2-(5,6-Dimethoxy-1H-2-benzimidazolylsulphinylmethyl)-N,N-dimethyl-benzenamine. mp 142–144°.
v) i) 5-(1H-2-B nzimidazolylthiomethyl)-N,N,2-trimethyl-4-pyrimidinamine. mp 174.5–176°.
ii) 5-(1H-2-B nzimidazolylsulphinylmethyl)-N,N,2-trim thyl-4-pyrimidinamine. mp 189–190.5°.
w) i) N,N-Dimethyl-2-(4-trifluoromethyl-1H-2-benzimidazolylthiomethyl)-benzenamine. mp 93–5°.

ii) N,N-Dimethyl-2-(4-trifluoromethyl-1H-2-benzimidazolylsulphinylmethyl)-benz namine. mp 129–130°.
x) i) N-[2-(1H-2-Benzimidazolylthio)ethyl]-N-methylbenzenamine. mp 115–7°.
ii) N-[2-(1H-2-Benzimidazolylsulphinyl)ethyl]-N-methyl-benzenamine. mp 148–149.5°.
y) i) N,N-Dimethyl-2-(1H-2-naphtho[2,3-d]imidazolylthiomethyl)-benzenamine. mp 178°(d).
ii) N,N-Dimethyl-2-(1H-2-naphtho[2,3-d]imidazolylsulphinylmethyl)-benzenamine. mp 129°(d).
z) i) 2-(2-(1H-Benzimidazolyl)sulphinyl)benzeneamine mp 202–203° shrinks at 160°.

Example 3
2-(1H-2-Benzimidazolylsulphinylmethyl)-N,N-dimethyl-6-propyl-benzeneamine.
a) *2-Methoxy-3-propylbenzoic acid*
Methyl 2-methoxy-3-propylbenzoate (1.9g) was dissolved in methanol (300ml). Sodium hydroxide (16.6g) in water (100ml) was added and the mixture was heated at reflux for three hours. The solvent was evaporated and the mixture acidified with dilute hydrochloric acid. The product was extracted with ethyl acetate (800ml), washed with water, dried over magnesium sulphate and the solvent evaporated. Extraction of the resulting brown oil with hot pentane yielded 25.9g of the sub-title compound as a yellow solid. mp 55–58°.

b) *N-(1,1-Dimethyl-2-hydroxyethyl)-2-methoxy-3-propyl benzamide*
2-Methoxy-3-propylbenzoic acid (25.3g) in dry dichloromethane (400ml) was heated at reflux temperature with thionyl chloride (17ml) for three hours and then stirred at room temperature for 14 hours. The solvent was evaporated and the product distilled using a Kugelruhr apparatus (air bath temperature 135°; 0.35mmHg) to yield 24.1g of a pale yellow oil. This oil was dissolved in dry dichloromethane (200ml) and added gradually to a stirred solution of 2-amino-2-methyl propanol (20.2g) in dichloromethane (200ml) at 0° under N_2. The reaction mixture was stirred at room temperature for 18 hours. The product was extracted with chloroform (300ml) and washed with dilute hydrochloric acid (150ml), sodium bicarbonate solution (150ml) and brine (100ml) and then dried over magnesium sulphate. After evaporation of the solvent the sub-title compound was crystallised from cyclohexane as a white solid (20.4g). mp 95–96.5°.

c) *4,5-Dihydro-2-[2-methoxy-3-propylphenyl]-4,4-dimethyloxazole*
The product from step (b) (20.4g) was stirred in dry dichloromethane (200ml) and cooled to 0°. Thionyl chloride (17ml) was added and the reaction mixture stirred at room temperature for two hours. The solvent and thionyl chloride were evaporated and the residue was treated with ether. Water was added to the solid and the mixture was basified with dilute sodium hydroxide solution. The product was extracted with ether (50ml), washed with brine (150ml) and dried over magnesium sulphate. The solvent was then evaporated and the product purified by flash chromatography, using 10% ethyl acetate/90% petroleum ether as eluant, and by distillation using a Kugelruhr apparatus (air bath temperature 135°; 0.7mmHg) to yield the sub-title compound (17g) as a colourless oil.

d) *2-(4,5-Dihydro-4,H-dimethyl-oxazol-2-yl)-N,N-dimethyl-6-propyl-benzeneamine*
Dimethylamine (9ml) was added to dry tetrahydrofuran (120ml) and the mixture cooled to −15° and stirred under N_2 during the addition of n-butyl lithium solution (81ml of 1.6M in hexane). The reaction mixture was stirred at −16° for 40 minutes. The product from step (c) (16g) in dry tetrahydrofuran (100ml) was added and the mixture allowed to warm to room temperature and then stirred for 20 hours. The reaction mixture was quenched with water and the product extracted with ethyl acetate (500ml), washed with brine (100ml) and dried over magnesium sulphate. The solvent was evaporated and the product distilled using a Kugelruhr apparatus (air bath temperature 135°; 0.25mmHg) to yield 16.4g of the sub-title compound as a pale yellow oil.

e) *2-Dimethylamino-3-propylbenzenemethanol*
The product from step (d) (17.3g) was heated at reflux in 2M dilute hydrochloric acid (480ml) for 20 hours. The solvent was evaporated and the residue dried over phosphorous pentoxide. This product was then dissolved in dry tetrahydrofuran (500ml), cooled in ice and stirred under N_2 during the addition of borane-tetrahydrofuran (300ml of 1M in tetrahydrofuran). The reaction mixture was stirred at room temperature for 68 hours and was then quenched with methanol. The solvent was evaporated and the product was extracted with ethyl acetate, washed with sodium bicarbonate solution (150ml) and with brine (150ml) and dried over magnesium sulphate. The solvent was evaporated and the product distilled using a Kugelruhr apparatus (air bath temperature 156°; 1.0mmHg) to yield the sub-title compound (13.2g) as a pale yellow oil.

f) *2-Chloromethyl-6-propyl-N,N-dimethylbenzeamine hydrochloride*

The product from step (e) (13.1g) was cooled to 0° in dry dichloromethane (50ml) and stirred during the addition of thionyl chlorid (6ml). The mixtur was heated at reflux for 1.5 hours. The solvent was evaporated and ethereal HCl added. The product was collected and then triturated with dry ether to yield 6.8g of the sub-title compound as a cream solid. Mass spectrum:– m/e 211/213.

g) *2-(1H-2-Benzimidazolylthiomethyl)-N.N-dimethyl-6-propyl benzeneamine*
The product of step (f) was converted to the sub-title compound (mp 147–150°) by the method of Example 1a.

h) *2-(1H-2-Benzimidazolylsulphinylmethyl)-N.N-dimethyl-6-propyl benzenamine*
The product of step (g) was converted to the title compound (mp 145–147.5°) by the method of Example 1b.

Example 4
By the method described in Example 3, and using the appropriate starting materials, may be prepared the following compounds:
a) i) 2-(1H-2-Benzimidazolylthiomethyl)-4-methoxy-N.N-dimethyl-benzenamine. mp 144–145°.
ii) 2-(1H-2-Benzimidazolylsulphinylmethyl)-4-methoxy-N,N-dimethyl-benzenamine. mp 130–131°.
b) i) 2-(1H-2-Benzimidazolylthiomethyl)-N-ethyl-N-propyl-benzenamine. mp 121°.
ii) 2-(1H-2-Benzimidazolylsulphinylmethyl)-N-ethyl-N-propyl-benzenamine. mp 114°.
c) i) 2-[2-(4-Morpholinyl)phenylmethylthio]-1H-benzimidazole. mp 170°.
ii) 2-[2-(4-Morpholinyl)phenylmethylsulphinyl]-1H-benzimidazole. mp 74–76°.

Example 5
2-(1.2.3.4-Tetrahydro-1.6-dimethylquinolin-8-ylmethylsulphinyl)-1H-benzimidazole
a) *1.2.3.4-Tetrahydro-6-methylquinoline*
6-Methylquinoline (5.16g; 36mmole) and pyridine/borane complex (13.2ml; 144mmole) in acetic acid (75ml) were stirred at room temperature for 18 hours. The product mixture was treated with dilute aqueous HCl (30ml) with stirring and then basified (40% NaOH, then $NaHCO_3$ to pH 8) and extracted with ethyl acetate (3x). The combined organics were washed with water (3x). dried (Na_2SO_4) and evaporated to yield a brown oil which was flash-chromatographed. Petroleum ether (bp 40–60°)/ether (3/1) yielded the sub-title compound as a low melting solid (4.7g 67%). m/e 147 (base peak).

b) *1,2,3 4-Tetrahydro-1,6-dimethylquinoline*
6-Methyltetrahydoquinoline (3.8g; 25.8mmole) in dry methylene chloride (75ml) was treated with trimethyloxonium fluoroborate (5.2g; 3.5mmole) and stirred at room temperature for 20 hours. The mixture was poured into saturated aqueous sodium hydrogen carbonate and the organic layer run off. The aqueous layer was extracted with $CHCl_3$ (2x). The combined organics were washed with water (2x), dried (Na_2SO_4) and evaporated to give a yellow oil which was flash-chromatographed. Petroleum ether (bp 40–60°)/ether (5/1) eluted the sub-titled compound as a pale yellow oil.

m/z 161 (MW = base peak), 160, 146, 145, 144, 131, 117, 91, 77.

c) *1,2,3,4-Tetrahydro-1,6-dimethylquinoline-8-carboxaldehyde*
Phosphorylchloride (1.17ml); 1.982g; 12.5mmole) was added dropwise to a solution of the product of step b) (2.1g; 10.3mmole) in dry dimethylformamide (7ml) under N_2 in an ice-bath with stirring. The reaction mixture was heated to 120° (momentarily) and then held at 80° for 2 hours. The mixture was cooled, poured into dilute aqueous $NaHCO_3$ and extracted with ethyl acetate (3x). The combined organics were washed with water (3x), dried ($NaSO_4$) and evaporated to yield the sub-title compound as a yellow oil 960mg (49%).
m/z 189 (m.w. = base peak), 172, 160, 144, 132, 117, 105, 91. 'HNMR ($CDCl_3$) aldehyde at δ 10.06.

d) *1,2,3,4-Tetrahydro-8-hydroxymethyl-1,6-dimethylquinoline*
S dium borohydrid (300mg; 7.94mmol) was added porti nwise to the product of step (c) (1.5g; 7.94mmole) in ethanol with stirring at room temperatur over 10 minutes. The mixtur was stirred for a further 20 minut s, poured into water, and extracted with thyl acetate (3x). The combined organics were washed with water (2x), dried (Na_2SO_4) and vaporated to give the sub-title compound as a viscous pale yellow oil 1.41g (93%).
m/z (mono TMS derivative) 263 (MW), 248 (base peak), 172, 73.

e) *1,2,3,4-Tetrahydro-8-chloromethyl-1,6-dimethylquinoline hydrochloride*

The product of step d) (1.4g; 7.33mole) in dry benzene (10ml) was treated portionwise with thionyl chloride (0.8ml; 1.31g; 11mmol) in a cold water-bath with stirring. Th mixtur was allowed to warm to room temperature (2 hours) and then heated at 50° (1 hour). It was then cooled again and treated with ethereal HCl (2ml) and evaporated to dryness. The resulting brown solid was triturated with ether and filtered off to yield the sub-title compound as a light brown solid 1.73g (96%).

m/z 209/11 (M.W.), 174 (base peak), 158, 145, 131, 119, 91.

f) *2-(1,2,3,4-Tetrahydro-1,6-dimethyl-quinolin-8-ylmethylthio)-1H-benzimidazole*

The product of step e) was converted to the sub-title compound (mp 85–88°d) by the method of Example 1a).

g) *2-(1,2,3,4-Tetrahydro-1,6-dimethylquinolin-8-ylmethylsulphinyl)-1H-benzimidazole*

The product of step f) was converted to the title compound (mp 112–3°) by the method of Example 1b).

Example 6

By the method described in Example 5, and using the appropriate starting materials, may be prepared the following compounds:

a) i) 2-(1H-2-Benzimidazolylthiomethyl)-N,N,3,4,5-pentamethyl-benzenamine. mp 161.5–162.5°.

ii) 2-(1H-2-Benzimidazolylsulphinylmethyl)-N,N,3,4,5-pentamethyl-benzenamine. mp 122–3°.

b) i) 2-(1H-2-Benzimidazolylthiomethyl)-4-methoxy-N,N,3,5-tetramethyl-benzenamine. mp 157–158°.

ii) 2-(1H-2-Benzimidazolylsulphinylmethyl)-4-methoxy-N,N,3,5-tetramethyl-benzenamine. mp 138–9°.

c) i) 2-(1H-2-Benzimidazolylthiomethyl)-N,N-dimethyl-4-(1,1-dimethylethyl)-benzenamine. mp 166–7°.

ii) 2-(1H-2-Benzimidazolylsulphinylmethyl)-N,N-dimethyl-4-(1,1-dimethylethyl)-benzenamine. mp 130°.

Example 7

2-[1-(2-Dimethylaminophenyl)ethylsulphinyl]-1H-benzimidazole

a) *1-(2-Dimethylaminophenyl)-ethanol*

A Grignard reagent was prepared from 2-bromo-N,N-dimethylaniline (10.0g) and magnesium (1.4g) in dry ether (60mls) with iodine (1 crystal). The reagent was cooled to 0° and stirred under a nitrogen atmosphere. A solution of acetaldehyde (3.34mls) in dry ether (20 mls) was added dropwise over 30 mins. After stirring at 0° for 1 hour the mixture was allowed to warm to room temperature. After a further 2 hours an aqueous solution of ammonium acetate was added. After 10 mins the layers were allowed to separate. The aqueous layer was extracted with ether and the combined ether extracts were washed with water and brine and then dried and evaporated to leave a dark yellow oil 7.5g. Flash chromatography (1:1 ether/petroleum ether) produced the required product as a clear yellow oil 3.7g.

NMR ($CDCl_3$) δ 7.2m (4H) 6.8broad (1H) 5.12q (1H) 2.73S(6H) 1.55d (3H)

b) *2-[1-(2-Dimethylaminophenyl)-ethylthio]-1H-benzimidazole*

A solution of 2-(2-dimethylaminophenyl)-ethanol (3.6g) in dry benzene (50mls) was cooled in an ice bath and thionyl chloride (1.75mls) was added dropwise. After stirring for 1 hour the mixture was warmed to room temperature and stirring continued for 2 hours. The mixture was concentrated *in vacuo* and azeotroped with benzene. The residue was taken up in dry dimethylformamide (50mls) and stirred. To this solution was added a solution of 2-mercaptobenzimidazole (3.22g) in dry dimethylformamide (30mls), followed by potassium carbonate (7.5g). The mixture was stirred at room temperature for 18 hours and then poured onto water containing brine, and extracted with ethyl acetate. The combin d xtracts wer washed with water and brine and then dried and evaporated to leave a pale brown solid 6.1g. Flash chromatography produced the product as a buff solid 3.4g NMR ($CDCl_3$) δ 7.0–7.7m(8H) 5.22q(1H) 2.95S(6H) 1.80d(3H)

c) *2-[1-(2-Dimethylaminophenyl)-ethylsulphinyl]-1H-benzimidazole*

A s lution of the product of step b) (3g) in ethyl acetate (350mls) was cooled to − 20° and a solution of metachloroperb nzoic acid (1.83) in ethylacetate (50mls) was added. After stirring for 1 hour the mixture was concentrated *in vacuo*. The resulting gum was dissolved in a minimum of dichloromethane and plac d on a flash chromatography column. Elution with 1:1

ether/petroleum ether produced r cover d starting material 1.5g plus both diastereomers of the title compound: Least polar diast reomer 437mg. mp 119–120°. Most polar diastereomer 298mg. mp 103–105°.

Example 8

2-(1H-Benzimidazol-2-ylsulphinylmethyl)-benzenethiol acetate

a) *2-Hydroxymethylthiophenol*

To a stirred ice cooled solution of thiosalicylic acid (3.08g) in dry tetrahydrofuran (20ml) under nitrogen was added a solution of borane tetrahydrofuran complex (40mls of IM in tetrahydrofuran) dropwise over 1 hour. The mixture was stirred at 0° for 1 hour. Methanolic hydrogen chloride was added dropwise until effervescence ceased. The mixture was poured onto water and extracted with ethyl acetate. The ethyl acetate was washed with dilute hydrochloric acid, water and brine and then dried and evaporated to leave the sub-title compound as a yellow oil (2.9g).

NMR ($CDCl_3$) δ 7.1–7.5m(4H) 4.75s(2H) 3.69bs(1H) 2.05bs(1H)

b) *2,2'-Dithiobisbenzenemethanol*

A solution of 2-hydroxymethylthiophenol (19g) was mechanically stirred with basic alumina (100mls) in ethanol (400mls) whilst oxygen was bubbled through for 48 hours. The alumina was removed by filtration and washed with hot ethanol. The ethanol was filtered and evaporated. The residue was crystallised from ethanol to give the sub-title compound as white prisms 9.33g, mp 136–8°.

c) *2,2'-Dithiobisphenylmethylchloride*

2,2'-Dithiobisbenzenemethanol (500mg) was cooled in a water bath and thionyl chloride (350 ul) added dropwise. The mixture was agitated occasionally over 45 minutes. The excess thionyl chloride was removed *in vacuo* and azeotroped with benzene to afford the sub-title compound as a clear yellow gum 570mg NMR ($CDCl_3$) δ 7.2–7.9m (8H) 4.72s (4H).

d) *2-(2,2'-Dithiobisphenylmethylthio)-1H-benzimidazole*

A solution of 2-mercaptobenzimidazole (510mg) in dry dimethylformamide (5mls) was added to a mixture of potassium carbonate (547mg) and 2,2'-dithiobisphenyl methyl chloride (570mg) in dry dimethylformamide (3mls). The mixture was stirred at room temperature for 3 days, poured onto water and the precipitate collected. The solid was washed with water then taken up in dichloromethane. The solution was dried and concentrated *in vacuo*. Flash column chromatography afforded the sub-title compound as a white solid 260mg NMR ($CDCl_3$) δ 7.1–7.6m (16H) 4.60s (4H).

e) *2-(1H-Benzimidazol-2-ylthiomethyl)-benzenethiol acetate*

An ice cooled suspension of 2-(2,2'-dithiobisphenylmethylthio)-1H-benzimidazole (11.5g) in ethanol (200mls) was stirred whilst sodium borohydride (806mg) was added portionwise over 30 minutes. The mixture was stirred for a further 60 minutes whilst warming to room temperature. The mixture was stirred at room temperature for 2 hours, acidified with ethanolic hydrogen chloride and stirred for 10 minutes. The mixture was then poured onto sodium bicarbonate solution and extracted with ethyl acetate. The extracts were washed with water and brine and then dried and concentrated *in vacuo*. The residue was taken up in dry dimethylformamide (80mls) and sodium bicarbonate (7.5g) added. The mixture was cooled to 0° and acetic anhydride (6.0mls) added slowly. The mixture was allowed to reach room temperature and was left for 18 hours. It was poured onto water and extracted with ethyl acetate. The ethyl acetate was washed with water and brine and then dried and evaporated. Flash chromatography produced crude product 3.1g. Crystallisation from ethyl acetate produced colourless prisms (1.5g) of the sub-title compound, mp 134–8°.

f) *2-(1H-Benzimidazol-2-ylsulphinylmethyl)-benzenethiol acetate*

The product of step e) was converted to the title compound (mp 65–8°) by the method of Example 1b).

Example 9

2-[(1-Acetyl-1H-benzimidazol-2-yl)sulphinylmethyl]-benzenethiol acetate

a) *2-[(1-Acetyl-1H-benzimidazol-2-yl)thiomethyl]-benzenethiol acetate*

2-(2,2'-Dithiobisph nylmethylthio)-1H-b nzimidazole (1g) was dissolved in ethanol (20mls) and stirr d at 0° under N_2. Sodium borohydrid (70mg) was added and the mixture stirred for 2 hours. The solution was acidified with ethanolic HCl, stirred for 5 minutes, poured onto sodium bicarbonate solution and extracted with ethyl acetate. The ethyl acetate was washed with sodium bicarbonate solution, water and brine and then dried and evaporated. The resulting oil

was dissolved in dry dimethylformamide and sodium bicarbonate (1.86g) added. The mixture was stirred under N_2 and cooled to 0°. Acetic anhydride (1.75mls) was added dropwise and the solution stirred at 0° for 1 hour. The mixture was poured onto water and extracted with ethyl acetat . The thyl acetate was washed with water and brine and then dried and evaporated. Flash chromatography produced the sub-title compound as a colourless solid 370mg. NMR ($CDCl_3$) δ 7.7m (3H). 7.25–7.5m (5H) 4.66s (2H) 2.78s (3H) 2.45s (3H).

b) *2-[(1-Acetyl-1H-benzimidazol-2-yl)-sulphinylmethyl]-benzenethiol acetate*

The product of step a) was converted to the title compound (mp 99–102°) by the method of Example 1b).

Example 10

2-(1H-2-Benzimidazolylsulphinyl)-N,N-dimethylethylamine

2-[2-(N,N-Dimethylamino)ethylthio]-3H-benzimidazole (1.7g; 7.7mmole), vanadyl (III) acetyl acetonate (200mg) and *t*-butylhydroperoxide (1.5g of 70% aqueous solution; 1.05g; 11.6mmole) in dry methylene chloride were stirred together under N_2 in an ice/water bath for 3 hours. Further aliquots of vanadyl acetyl acetonate (200mg) were added after 40 minutes and two hours. The mixture was evaporated to dryness (rotary evaporator at room temperature) and immediately flash-chromatographed using chloroform/methanol (5/l) as eluant.

The title compound was obtained as a pale yellow oil (700mg; 38%).

'HNMR ($CDCl_3$, 360MH_2) δ 7.7(m,2H); 7.34(m,2H); 3.52 (m, 1H); 3.35 (m,1H); 2.97 (m,1H); 2.81 (m,1H); 2.35 (2.6H).

Example 11

3-(1H-2-Benzimidazolylsulphinylmethyl)-N,N-dimethyl-2-pyridineamine

a) *Ethyl 2-dimethylamino-3-pyridinecarboxylate*

Ethyl 2-chloro-3-pyridine carboxylate (14.9g) in dry tetrahydrofuran (100ml) was treated with dimethylamine (15ml) at 0° with stirring. The reaction mixture was then stirred at room temperature for 20 hours. The solvent was evaporated and the product was extracted with ethyl acetate (400ml), washed with aqueous sodium bicarbonate solution (100ml) and with brine (100ml) and dried over magnesium sulphate. The solvent was evaporated and the product distilled using a Kugelruhr apparatus (air bath temperature 137°; 1.1mmHg) to yield 15.4g of the sub-title compound as a pale yellow oil.

b) *2-Dimethylamino-3-pyridinemethanol*

Lithium aluminium hydride solution (44.2ml of 1M in ether) was added gradually to a solution of the product of step a) (7.8g) in dry tetrahydrofuran (150ml) at 0° with stirring under N_2. The mixture was heated at reflux for 1.5 hours and then quenched with ice water. The product was extracted with ethyl acetate (500ml), washed with brine (2 × 100ml), dried over magnesium sulphate and the solvent evaporated. The product was distilled using a Kugelruhr apparatus (air bath temperature 105°; 0.4mmHg) to yield 5.65g of the sub-title compound as a pale yellow oil.

c) *3-Chloromethyl-2-[N,N-dimethylamino]pyridine hydrochloride*

Thionyl chloride (3.25ml) was added dropwise to a stirred solution of the product of step b) (5.65g) in dry dichloromethane (100ml) at 0° under N_2 of nitrogen. The reaction mixture was allowed to warm to room temperature and then heated at reflux for 1.5 hours. The solvent was evaporated and the product was azeotroped with toluene and triturated with ether. The residue, a white solid, was the sub-title compound (7.16g). mp 190–192°.

d) *3-(1H-2-Benzimidazolylthiomethyl)-N,N-dimethyl-2-pyridineamine*

The product of step c) was converted to the sub-title compound (mp 106–9°) by the method of Example 1a).

e) *3-(1H-2-Benzimidazolylsulphinylmethyl)-N,N-dimethyl-2-pyridineamine*

The product of step d) was converted to the subtitle compound (mp 124–6°) by the method of Example 1b).

Example 12

2-(1H-2-Benzimidazolylsulphinylmethyl)-phenol

a) *(2-(1H-2-Benzimidazolylthiomethyl)-phenol*

To a stirred ice cold suspension of 2-hydroxy benzyl alcohol (24.8g) in dry benzene (60mls) was added thionyl chloride (16mls) dropwis ov r 20 minutes. The soluti n was allowed to warm to room temperature where it was k pt for 1 hour. The mixture was oncentrated *in vacuo* to afford crud 2-chloromethylphenol.

To a stirred solution of 2-mercaptobenzimidazole (16g) in dry dimethylformamide (200mls) under nitrogen was added potassium carbonate (35g) and the mixture stirred for 20 minutes. The crude 2-chloromethylphenol was dissolved in dry dimethylformamide (80mls) and added to the above mixture. The resulting mixture was stirred at room temperature for 20 hours, poured onto water containing brine and extracted with ethyl acetate. The combined ethyl acetate extracts were washed with water and brine and then dried and evaporated. Flash chromatography produced a white solid 4.5g.

Crystallisation from ethyl acetate gave the sub-title compound as colourless prisms 1.5g. NMR ($CDCl_3$) δ 7.46bs (2H) 7.2m (5H) 6.99d (1H) 6.89t (1H) 4.47s (2H).

b) *(2-(1H-2-Benzimidazolylsulphinylmethyl)-phenol*

To an ice cooled solution of (2-hydroxyphenyl)-methylthio-1H-benzimidazole (100mg) in chloroform (30mls) was added an ice cold solution of *m*-chloroperenzoic acid (72mg) in dichloromethane (10mls). The mixture was stirred at 0° for 1 hour and then allowed to warm to room temperature. After 3 hours the mixture was diluted with chloroform, washed with sodium bicarbonate solution, sodium metabisulphite solution and water and then concentrated *in vacuo* to leave the title compound as a colourless solid 75mg. NMR DMSO δ 7.8m (2H) 7.5m (4H) 6.9m (2H) 4.53 dod (2H).

Example 13

2-[2-Pyridinylmethylsulphinyl-N-oxide]-1H-benzimidazole

a) *2-Chloromethylpyridine-N-oxide*

An aqueous solution of 2-chloromethylpyridine hydrochloride (1.64g) was basified with sodium bicarbonate and extracted with chloroform (2 × 15mls). The chloroform was washed with water and brine and then dried and filtered. The solution was stirred under nitrogen and m-chloroperbenzoic acid (1.81g) added portionwise over a period of 20 minutes. After stirring at room temperature for 18 hours the mixture was poured onto saturated sodium bicarbonate solution, extracted with chloroform and the combined chloroform extracts were concentrated *in vacuo* to afford the sub-title compound as a yellow oil which solidified on standing, 1.31g. NMR ($CDCl_3$) δ 8.3m (1H) 7.7m (1H) 7.3m (2H) 4.86s (2H).

b) *2-[2-Pyridinylmethylthio-N-oxide)]-1H-benzimidazole*

The product of step a) was converted to the sub-title compound (mp 148–151°) by the method of Example 1a).

c) *2-[2-Pyridinylmethylsulphinyl-N-oxide]-1H-benzimidazole*

The product of step b) was converted to the title compound (mp 183–4° (d)) by the method of Example 1b).

Example 14

[2-(2-Dimethylaminophenylmethylsulphinyl)-1H-benzimidazol-1-yl]methyl-2,2-dimethylpropanoate

A solution of 2-(1H-2-benzimidazolylsulphinylmethyl)-N,N-dimethylbenzeamine (1.5g 5mM) and chloromethylpivalate (1ml 6.9mM) in dry dimethylformamide (20ml) containing anhydrous potassium carbonate (1.4g 10,0mM) was stirred at 25° for 16 hours. The mixture was quenched with water (50ml) and extracted with ethyl acetate (3 × 100ml). The organic phase was washed with brine (2 × 25ml), dried over magnesium sulphate, filtered and evaporated to leave a yellow oil which was purified by flash chromatography eluting with dichloromethane/ethyl acetate (5:1). The required fractions were evaporated to leave a yellow oil which solidified on standing. The solid was triturated with pentane, filtered and dried under vacuum (1.2g); mp 70–71°.

Similarly prepared were:–

1. Ethyl 2-(2-dimethylaminophenylmethylsulphinyl)-1H-1-benzimidazole carboxylate hemihydrate. mp 75–77°.
2. 2-[1-Methyl-(1H-2-benzimidazolylsulphinylmethyl)]-N,N-dimethylbenzeneamine. ms: m/e 313.

Example 15

N,N-Dimethyl-2-[5-(4-methylphenylsulphonyl)-1H-2-benzimidazolylsulphinylmethyl]benzenamine

a) *5-(4-Methylphenylsulphonyl)-1H-benzimidazole-2(3H)-thione*

4-Toluenesulphonylbenzene-1,2-diamine (2.6g) was dissolved in dimethylformamide (50ml) and treated at 60° with carbon disulphide (6ml) under nitrogen for 18 hours. The cooled solution was poured into ice-water to afford a yellow precipitate of the subtitle compound. mp 200°.

b) *N,N-Dimethyl-2-[5-(4-methylphenylsulphonyl)-1H-2-benzimidazolylthiomethyl]benzenamine*
The product of step a) was converted to the sub-title compound (mp 81°) by the method of Example 1a).

c) *N,N-Dimethyl-2-[5-(4-methylphenylsulphonyl)-1H-2-benzimidazolylsulphinylmethyl] benzenamine*
The product of step b) was converted to the title compound (mp 85°) by the method of Example 1b).

Example 16
By a similar method to that of Example 15 the following compounds were prepared:
a) i) 2-(4,7-Dimethoxy-1H-2-benzimidazolylthiomethyl)-N,N-dimethyl-benzenamine. mp 142–144°.
ii) 2-(4,7-Dimethoxy-1H-2-benzimidazolylsulphinyl methyl)-N,N-dimethyl-benzenamine. mp 61°.

Example 17
2-(1H-2-Benzimidazolylsulphinylmethyl)benzeneamine
a) *N-(2-Hydroxymethylphenyl)-2,4,6-triethylbeneze sulphonamide*
a solution of (2-([(2,4,6-trimethylphenyl)sulphonyl]amine)benzoic acid (5.0g) in dry tetrahydrofuran (80ml) was stirred in an ice bath under nitrogen and treated with diborane-tetrahydrofuran complex (17.3ml, of a 1 molar solution). The reaction mixture was stirred for 3 hours at room temperature cooled to 0° and more diboran-tetrahydrofuran complex (17.3ml, 1 molar solution) added and stirring continued at room temperature overnight. The reaction was again cooled to 0°, more diboran-tetrahydrofuran complex (17.3ml, 1 molar solution) added and stirring continued at room temperature for 3 hours. Dilute hydrochloric acid was added continuously and the mixture diluted with water and extracted with ethyl acetate which was washed with water and dried over magnesium sulphate. The solvent was evaporated to give 4.0g of the required product as an oil. The structure was confirmed by nmr and ms.

b) *N-[2-Chloromethylphenyl)-2,4-6-trimethylbenzenesulphonamide*
The product of step a) (4.0g) in dry dichloroethane (80ml) was treated with thionyl chloride (1.15ml) at room temperature with stirring. The reaction mixture was stirred for 5 hours, more thionyl chloride (0.1ml) was added and stirring continued overnight. The reaction mixture was then poured into water, and the organic layer separated. The aqueous layer was washed with dichloromethane and the organic solutions combined, dried over magnesium sulphate and the solvent evaporated to give 4.06g of the sub-title compound as a pale yellow oil.

c) *N-[2-(1H-2-Benzimidazolylthiomethyl)phenyl]-2,4,6-trimethylphenylsulphonamide*
The product of step b) (4.06g) and 1,3-dihydro-2H-benzimidazole-2-thione (1.9g) were stirred with anhydrous potassium carbonate (2.1g) in dry dimethylformamide (70ml) for 3 hours. The reaction mixture was poured into water and the precipitated product collected by filtration, washed well with water and dried to give 4.39g of the required product as a buff coloured powder. mp 202–203°.

d) *2-(1H-2-Benzimidazolylthiomethyl)benzeneamine*
The product of step c) (3.87g) and anisole (4.83ml) were treated at room temperature with methanesulphonic acid (29ml) with stirring. The deep red reaction mixture was stirred for 27 hours, poured slowly into an excess of aqueous sodium bicarbonate solution and extracted with ethyl acetate, which was then washed with brine and dried. The solvent was evaporated and the residue eluted down a flash chromatography column using dichloromethane/ethyl acetate (4:1) as eluant to give 1.43g of the required product as a light brown solid. mp 270° (melts at 139° and resolidifies).

e) *2-(1H-2-Benzimidazolylsulphinylmethyl)benzenamine*
The product of step d) was oxidised in the same manner as in Example 1b, to give, after recrystallisation from ethanol, the title compound as a fluffy colourless solid. mp 177°(d).

Example 18
2-(5-Amino-1H-2-benzimidazolylsulphinylmethyl)-N,N-dimethyl-benzenamine
N,N-Dimethyl-2-(5-nitro-1H-2-benzimidazolylsulphinylmethyl)benzenamine (2.2g) was hydrogenated in ethanol (150) containing PtO_2(0.4g) under 1 atmosphere pressure for 24 hours. The catalyst was removed, and solvent evaporated *in vacuo*. The residue was chromatographed (SiO_2/1:10 methanol-ethyl acetate) to afford the title compound. mp 156–7°(d).

Example 19

2-(1H-2-Benzimidazolylsulphinylmethyl)-N-cyclohexyl-N-methyl-benzeamine

a) *2-(N-Cyclohexyl-N-methyl-amino)benzaldehyde*

o-Fluorobenzaldehyde (8.68g) and N-methylcyclohexylamine (11.9g) were heated under reflux in dimethyl formamide (70ml) containing potassium carbonate (14.49g) with stirring for 5.5 hours. The cooled reaction mixture was poured into dilute HCl and extracted into $CHCl_3$. The aqueous layer was separated and basified with potassium carbonate and extracted into $CHCl_3$, which was then washed with water, dried and evaporated, to afford the sub-title compound (11.8g). MS:M^+217 BP 174.

b) *2-(N-Cyclohexyl-N-methylamino)benzene methanol*

The product of step a) was reduced by the method of Example 5d) to afford the sub-title compound. MS M^+219 BP 148.

c) *2-(1H-2-Benzimidazolylthiomethyl)-N-cyclohexyl-N-methyl-benzenamine*

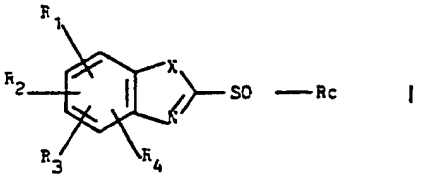
The product of step b) was converted to the sub-title compound by the method of Example 5. mp 165–166°.

d) *2-(1H-2-Benzimidazolylsulphinylmethyl)-N-cyclohexyl-N-methyl-benzeneamine*

The product of step c) was converted to the title compound by the method of Example 1b). mp 132–133°. 1000J(ir)/jaa

CLAIMS

1. A compound of formula I,



I

in which Rc is a nucleophilic nitrogen, oxygen or sulphur separated from the SO group by 1, 2, 3, 4 or 5 other atoms,

R_1, R_2, R_3 and R_4, which may be the same or different, are each hydrogen, halogen, alkoxy, alkyl, fluoroalkyl, alkanoyl, $RS(O)_n$–, $-NO_2$, $-N(R)_2$, –NHCOR, or –COOH or an ester or amide thereof,

or an adjacent pair of R_1, R_2, R_3 and R_4 may in addition to the values given above, together form a chain $-(CH_2)_x-$ or, together with the carbon atoms to which they are attached, form a 6 membered unsaturated carbocylic or nitrogen heterocyclic ring,

x is 3, 4 or 5,

n is 0, 1 or 2,

X is O, S or NR_{15},

R_{15} is hydrogen, –COR, –COOR or alkyl which latter is optionally substituted by –OCOR,

R is hydrogen, phenyl, or alkyl optionally substituted by phenyl, the phenyl groups in turn optionally being substituted by alkyl,

provided that i) Rc is not $-CH_2CH_2$-morpholino, ii) that when Rc is a nitrogen nucleophile carried on an aryl or heteroaryl group R_{15} is not a group –COR in which R is unsubstituted alkyl, iii) when X is NR_{15} Rc does not comprise an unsaturated nitrogen heterocyclic ring other than such a ring substituted by either a) a substituted or unsubstituted amino group, or b) an N-oxido group, and iv) when X is NR_{15} Rc does not comprise an alkyl group substituted by an optionally alkyl or halo substituted piperidino group,

and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein the nucleophile is separated from the SO group by 2 or 3 atoms.

3. A compound according to claim 1 or 2, wherein the nucleophile is more nucleophilic than water.

4. A compound according to any one of the preceding claims, wherein the nucleophile is basic.

5. A compound according to any one of the preceding claims, wherein the nucleophil is the oxygen of pyridine oxide or phenolic OH, or the sulphur of a thioether or of a thiophenol or of a precursor therefor.

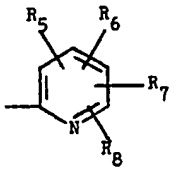
6. A compound according to any one of claims 1 to 4, wherein the nucleophile is a nitrogen nucleophile.

7. A compound according to claim 6, wherein the nitrogen nucleophile is in the form of an

xim , hydrazine, pyridine or amin .

8. A compound according to claim 7, wh rein th nitrogen nucleophile is an amin .

9. A compound according to claim 1, wherein Rc is a group of formula $-(CR_{16}R_{17})_y-(CR_{18}R_{19})_z-Rx$ in which y and z, which may be the same f different, are each 0, 1 or 2, R_{16}, R_{17}, R_{18} and R_{19}, which may be the same or different, are each hydrogen or alkyl, and Rx is a ring of formula II, III, IV or V,



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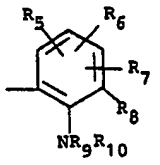

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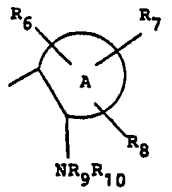
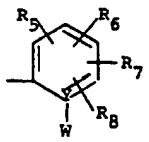


IV



V

and, when y + z is not 0, Rx may be $-NR_8R_{10}$,

R_5, R_6, R_7 and R_8 are selected from the significances defined in claim 1 for R_1, R_2, R_3 and R_4,

R_9 and R_{10}, which may be the same or different, are each hydrogen, alkyl, phenyl or cycloalkyl each of which may optionally be substituted by phenyl, the phenyl groups in turn optionally being substituted by alkyl,

or one of R_9 and R_{10} may be as defined above and the other may be $-OR_{11}$ or $-NR_{12}R_{13}$, or R_9 and R_{10}, together with the nitrogen atom to which they are attached may form a saturated or unsaturated 4 to 8 inclusive membered ring which may contain 0, 1 or 2 further hetero atoms, which ring may carry one or more substituents R_1, and R_{11}, R_{12} and R_{13} which may be the same or different, each represent hydrogen, alkyl optionally substituted by halogen or by =O, cycloalkyl, alkanoyl, phenyl or pyridyl,

or R_9 is as defined above save that it cannot form a ring with R_{10}, and R_8 and R_{10}, together with the nitrogen atom and the carbon atoms of the ring to which the nitrogen atom and R_8 are attached form a 4 to 8 inclusive membered ring which may contain 0, 1, or 2 further het ro atoms, which ring may carry one or m re substituents R_1,

A represents a 5 or 6 membered nitrogen or sulphur containing heterocyclic ring which is c nnect d to the r st of th mol cule through a ring carb n at m,

Y is N or C,

when Y is N, W is O^- and when Y is C then W is $-OH$ or $-SR_{14}$, and

R_{14} is hydrogen, phenyl, cycloalkyl, alkanoyl or alkyl optionally substituted by phenyl.

10. A compound acc rding to claim 9, wherein at least one of R_1, R_2, R_3 and R_4, and at least one of R_5, R_6, R_7 and R_8 is other than hydrogen.

11. A compound according to claim 9 or 10, wherein wh n any of R_1 to R_8, R, X, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18} or R_{19} represent or contain a carbon containing group that group contains up to and including 10 carbon atoms.

12. A compound according to claim 11, wherein that group contains up to and including 6 carbon atoms.

13. A compound according to any one of claims 9 to 12, wherein each of R_9 and R_{10} contain 1 or 2 carbon atoms.

14. A compound according to any one of claims 9 to 12, wherein R_9 and R_{10} together with the nitrogen atom to which they are attached form a ring, which contains a further nitrogen, oxygen and/or sulphur atom.

15. A compound according to claim 14, wherein the ring is a piperidino or morpholino ring.

16. A compound according to any one of claims 9 to 15, wherein ring A is aromatic.

17. A compound according to claim 16, wherein ring A is a pyridine or pyrimidine ring.

18. A compound according to any one of claims 9 to 17, wherein when any of R_1 to R_8 represent an ester the ester is with a C1 to 6 alkanol.

19. A compound according to any one of claims 9 to 18, wherein when any of R_1 to R_8 represent an amide they are an unsubstituted or a mono- or di-alkyl substituted amide.

20. A compound according to any one of claims 9 to 19, wherein an adjacent pair of R_1 to R_4 or of R_5 to R_8 together form a chain $-CH=CH-CH=CH-$ or $-(CH_2)_4-$.

21. A compound according to any one of the preceding claims wherein R_1 to R_4 are hydrogen, methoxy carbonyl, phenylcarbonyl, methyl, chloro, methoxy, CF_3, NO_2, *p*-toluenesulphonyl or $-NH_2$ or an adjacent pair of R_1 to R_4 together form a $-CH=CH-CH=CH-$ chain.

22. A compound according to any one of claims 9 to 21, wherein y is 0 and z is 0 or 1.

23. A compound according to any one of claims 9 to 22, wherein R_{16}, R_{17}, R_{18} and R_{19} are H or methyl.

24. A compound according to any one of claims 9 to 23, wherein R_5 to R_8 are hydrogen, methyl, chloro, propyl, methoxyl or butyl.

25. A compound according to any one of claims 9 to 24, wherein R_8 and R_{10} together form a piperidino ring.

26. A compound according to any one of the preceding claims, wherein X is NH, O, S, Nacetyl, NCH_2OCOt-butyl, NCOOethyl or Nmethyl.

27. A compound according to claim 9, wherein R_{14} is acetyl.

28. N,N-Dimethyl-2-(1H-benzimidazol-2-ylsulphinylmethyl)benzenamine.

29. 2-(2-Pyridinylmethylsulphinyl)benzoxazole.

30. 2-(4-Methoxy-3,5-dimethyl-2-pyridinylmethylsulphinyl)benzoxazole.

31. 2-(4-Methoxy-3,5-dimethyl-2-pyridinylmethylsulphinyl)benzothiazole.

32. 5-Chloro-2-(2-pyridinylmethylsulphinyl)benzoxazole.

33. Methyl 2-(2-pyridinylmethylsulphinyl)benzoxazole-5-carboxylate.

34. 2-(2-Pyridinylmethylsulphinyl)benzothiazole.

35. N,N-Dimethyl-2-(5,6-dimethyl-1H-2-benzimidazolylsulphinylmethyl)benzenamine.

36. 2-(1H-2-Benzimidazolylsulphinylmethyl)-N,N,4-trimethyl-benzenamine.

37. 2-(1H-2-Benzimidazolylsulphinylmethyl)-4-chloro-N,N-dimethyl-benzenamine.

38. 2-(5-Chloro-1H-2-benzimidazolylsulphinylmethyl)-N,N-dimethyl-benzenamine.

39. 2-(5,6-Dichloro-1H-2-benzimidazolylsulphinylmethyl)-N,N-dimethyl-benzenamine.

40. Methyl 2-(2-dimethylaminophenylmethylsulphinyl)-1H-benzimidazole-5-carboxylate.

41. N,N-Dimethyl-2-(5-methyl-1H-2-benzimidazolylsulphinylmethyl)benzenamine.

42. 2-[2-(1-Piperidyl)-phenylmethylsulphinyl]-1H-benzimidazole.

43. 2-(1H-2-Benzimidazolylsulphinylmethyl)-N,N-diethyl-benzenamine.

44. 2-[2-(5-Methoxy-1H-benzimidazolyl)sulphinylmethyl]-N,N-dimethyl-benzenamine.

45. 2-(2-Benzothiazolylsulphinylmethyl)-N,N-dimethyl-benzenamine.

46. 2-(5-Trifluoromethyl-1H-2-benzimidazolylsulphinylmethyl)-N,N-dimethyl-benzenamine.

47. N,N-Dimethyl-2-(5-nitro-1H-2-benzimidazolylsulphinylmethyl)-benzenamine.

48. [2-(2-N,N-Dimethylaminophenylmethylsulphinyl)-1H-5-benzimidazolyl]phenyl methanone.

49. 2-(5,6-Dimethoxy-1H-2-benzimidazolylsulphinylmethyl)-N,N-dimethyl-benzenamine.

50. 5-(1H-2-Benzimidazolylsulphinylmethyl)-N,N,2-trimethyl-4-pyrimidinamine.

51. N,N-Dimethyl-2-(4-trifluoromethyl-1H-2-benzimidazolylsulphinylmethyl)-benz namine.

52. N-[2-(1H-2-Benzimidazolylsulphinyl)ethyl]-N-methylbenzenamine.

53. N,N-Dim thyl-2-(1H-2-naphtho[2,3-d]imidazolylthiomethyl)-benz namine.

54. 2-(2-(1H-Benzimidazolyl)sulphinyl)benzeneamine.

55. 2-(1H-2-Benzimidazolylsulphinylmethyl)-N,N-dimethyl-6-propyl-benzenamin .

56. 2-(1H-2-Benzimidazolylthiomethyl)-N-ethyl-N-propyl-benz namine.

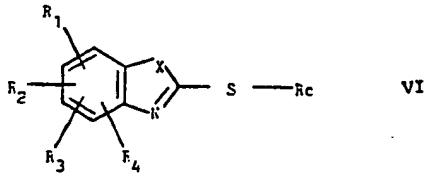
57. 2-(1H-2-Benzimidazolylsulphinylmethyl)-N-ethyl-N-propyl-benzenamine.

58. 2-[2-(4-Morpholinyl)ph nylmethylsulphinyl]-1H-benzimidazole.

59. 2-(1,2,3,4-Tetrahydro-1,6-dimethylquinolin-8-ylmethylsulphinyl)-1H-benzimidazole.

60. 2-(1H-2-Benzimidazolylsulphinylmethyl)-N,N,3,4,5-p ntamethyl-benzenamine.
61. 2-(1H-2-Benzimidazolylsulphinylmethyl)-4-methoxy-N,N,3,5-tetramethyl-benzenamine.
62. 2-(1H-2-Benzimidazolylsulphinylm thyl)-N,N-dim thyl-4-(1,1-dimethylethyl)-benzenamine.
63. 2-[1-(2-Dimethylaminophenyl)ethylsulphinyl]-1H-benzimidazole.
64. 2-(1H-Benzimidazol-2-ylsulphinylmethyl)-benzenethiol acetate.
65. 2-[(1-Acetyl-1H-benzimidazol-2-yl)sulphinylmethyl]benzenethiol acetate.
66. 2-(1H-2-Benzimidazolylsulphinyl)-N,N-dimethylethylamine.
67. 3-(1H-2-Benzimidazolylsulphinylmethyl)-N,N-dimethyl-2-pyridineamine.
68. 2-(1H-2-Benzimidazolylsulphinylmethyl)-phenol.
69. 2-[2-Pyridinylmethylsulphinyl-N-oxide)-1H-benzimidazole.
70. [2-(2-Dimethylaminophenylmethylsulphinyl)-1H-benzimidazol-1-yl]methyl-2,2-dimethylpropanoate.
71. Ethyl 2-(2-dimethylaminophenylmethylsulphinyl)-1H-1-benzimidazole carboxylate.
72. 2-[1-Methyl-(1H-2-benzimidazolylsulphinylmethyl)]-N,N-dimethylbenzeneamine.
73. N,N-Dimethyl-2-[5-(4-methylphenylsulphonyl)-1H-2-benzimidazolylsulphinylmethyl]-benzenamine.
74. 2-(4,7-Dimethoxy-1H-2-benzimidazolylsulphinylmethyl)-N,N-dimethyl-benzenamine.
75. 2(1H-2-Benzimidazolylsulphinylmethyl)benzeneamine.
76. 2-(5-Amino-1H-2-benzimidazolylsulphinylmethyl)-N,N-dimethyl-benzenamine.
77. 2-(1H-2-Benzimidazolylsulphinylmethyl)-N-cyclohexyl-N-methyl-benzeamine.
78. A compound according to any one of the preceding claims in the form of a pharmaceutically acceptable salt thereof.
79. A pharmaceutical formulation comprising a compound according to any one of the preceding claims in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.
80. A composition according to claim 79 which is enteric coated.
81. The pharmaceutical use of a compound of formula I as defined in claim 1 but without proviso ii), or a pharmaceutically acceptable salt thereof.
82. The use of a compound of formula I as defined in claim 1, but without provisos i) and ii) to make a pharmaceutical formulation for use in the prevention or inhibition of gastric acid secretion.
83. A process for the production of a compound of formula I, as defined in claim 1 or a pharmaceutically acceptable salt thereof, which comprises

a) selective oxidation of a corresponding compound of formula VI,



VI

in which R_1, R_2, R_3, R_4, X and Rc are as defined above,

b) production of a compound of formula I in which X is NR_{15} and R_{15} is as defined above save that it cannot be hydrogen, by reaction of a corresponding compound of formula I in which R_{15} is hydrogen with a compound $R_{15}Z$ in which R_{15} is as defined above save that it cannot be hydrogen, and Z is a good leaving group, or

c) production of a compound of formula I carrying an $-NH_2$ group by selective reduction of a corresponding compound of formula I carrying an $-NO_2$ group,

and where desired or necessary converting the resulting compound of formula I to a pharmaceutically acceptable salt thereof, or vice versa.

84. A process according to claim 83 and substantially as hereinbefore described.
85. A process according to claim 83 and substantially as hereinbefore described in any one of the Examples.
86. A compound of formula I, or a pharmaceutically acceptable salt thereof, whenever prepar d by a process according to any one of claims 83 to 85.
87. A compound of formula VI as defined in claim 83.
88. A compound according to claim 87, wher in Rc is as defined in claim 9 and y + z is more than 0.
89. A compound according to claim 88, wherein Rx is a ring of formula II.

CLAIMS

Amendments to th claims have been filed, and have the following effect:-

Claims 55, 69 and 77 above have be n deleted or textually amended.

New or textually amended claims have been filed as follows:–

55. 2-(1H-2-B nzimidazolylsulphinylmethyl)-N,N-dimethyl-6-propyl-benzenamine.

69. 2-(2-Pyridinylmethylsulphinyl-N-oxide)-1H-benzimidazole.

77. 2-(1H-2-Benzimidazolylsulphinylmethyl)-N-cyclohexyl-N-methyl-benzenamine.

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